REMARKS

Claims 13 and 16-23 are being examined on the merits. Claim 13 has been amended at the request of the Examiner for grammatical reasons and to claim a method for preparing insulin analogs which retain insulin activity according to the invention.

All pending claims were rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being indefinite in a Final Office Action. No other rejection is pending. The Examiner found claim 13 "vague, indefinite and confusing in the recitation of 'an insulin and an analog thereof.'" (2/9/04 Office Action, page 2.) The Examiner also found claim 13 "vague, indefinite and confusing in the recitation wherein of a reaction wherein preproinsulin produces an analog of insulin." (Id.) Applicant's remarks below respectfully traverse this rejection

Claim 13 is definite in its recitation of "insulin or an analog thereof." The term "insulin or analog thereof" is well understood by those of ordinary skill in the art. An analog of insulin is a compound related to human insulin where the order of the amino acids that make up human insulin has been altered. (See e.g., R. Mandosa, Insulin Analogs: Genetic Engineering for Diabetes Control, *Diabetes Wellness Letter*, Nov. 1998, pages 1-3.) For example, the first approved human insulin analog, known as Humalog or Lispro, has the amino acids lysine and proline at different positions on the beta chain of the insulin molecule compared with human insulin. (See Id.) Another insulin analog known prior to the filing date of the instant application was Lantus[1] which

[1] Lantus in now commercially available. See Exhibit 1 from the FDA Orange Book found at www.accessdata.fda.gov/scripts/cder/ob/docs/temptn.cfm.

"differs from human insulin in three amino acids." (See Id.) Further, evidence of the use of the term "insulin analog" in the art can be found in U.S. Patent No. 5,547,929 which is directed to insulin analog formulations. The '929 patent teaches that monomeric insulin analogs, also referred to as insulin analogs, can be readily prepared. (Col. 3, lines 2-18.) The patent further teaches that a number of modifications for making insulin analogs are widely accepted in the art. (Col 3, lines 19-29.)

The specification uses the term insulin analog in the same manner as it is used by those of ordinary skill in the art noted above. Indeed, the specification teaches at page 3, paragraph 5, the class of structures that are insulin analogs within the scope of the invention. More specifically, it teaches that "by substitution or absence of at least one naturally occurring amino acid residue and/or addition of at least one amino acid residue to the A and/B chain of the naturally occurring insulin" one may obtain an insulin analog. Contrary to the Examiner's statement that Applicant's specification merely discusses how to derive insulin analogs, the specification teaches that the result of the operation above results in insulin analogs which is entirely consistent with how that term is used in the art.

The Examiner further states that "nothing on this record discloses or suggests that an analog having a large portion thereof substituted by unrelated naturally occurring amino acid residues would be cleaved by the same one or more enzymes as the native protein, or that such an analog would retain insulin activity." (2/9/04 Office Action page 3.) In response to the Examiner's rejection, Applicant has amended Claim 13 to claim a process for preparing insulin analogs according to the invention wherein the analogs retain insulin activity. Support for this claim amendment cam be found at page 3 of the

specification at lines 22-26. Accordingly, the claim is now also directed to analogs of insulin that retain activity which the same activity as human insulin. For instance, with respect to insulin activity, Lantus differs from human insulin by three amino acids and has shown to be effective in humans. (See note 1 *supra.)* Accordingly, it is well known in the art that multiple amino acid substitutions can produce effective human insulin analogs that still retain insulin activity.

Applicant has further shown the invention operates to make di– and mono-Arg. (See Examples 4 and 5.) The Examiner, by comparison, provides no basis for the suggestion that analogs could not be cleaved according to the invention. The specification teaches that an object of the invention is for the enzymatic obtainment of insulin and their analogs, (see pages 2-3 of the Specification) and Applicant has demonstrated the invention operates as per the claims.

Because the term "insulin or an analog thereof" is clear and unambiguous, Applicant further traverses the Examiner's rejection related to "the reaction wherein preproinsulin produces an analog of insulin." Insulin analogs are well understood by those skilled in the art and, therefore, such individuals would understand what is meant in Claim 13 when the enzymes bonded to the support "cause a reaction in which an insulin or an analog thereof" is cleaved and recovered.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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